REMARKS

AMENDMENTS TO THE SPECIFICATION

The Title of the specification was amended to delete the " NOVEL" term to overcome the Examiners objection to the same. No new matter has been added.

The instant specification was replaced with a Substitute Specification to correct the various "SEQ ID NO:X" and "SEQ ID NO:Y" references objected to by the Examiner, in addition to the deletion of any hyperlinks, as well as to correct a variety of other minor typographical and grammatical errors identified by Applicants, including the substitution of each reference to ATCC Deposit NO:Z with the correct ATCC Deposit NO: "PTA-3161", for example. Each amendment has been either underlined or denoted using strike-through formatting, in accordance with 37 CFR 1.125(c), as applicable. All substantive amendments specifically listed and addressed herein have also been included in the Substitute Specification for the convenience of the Examiner.

Table I beginning on page 53, line 5 was amended to delete the "X" term in the "NT SEQ ID. No. X" column to make this table consonant with the other amendments made to the specification. Table I was further amended to delete the "Y" term in the "AA Seq ID No. Y" column to make this table consonant with the other amendments made to the specification. Table I was further amended to delete the "Z" term in the "ATCC Deposit No. Z and Date" column to make this table consonant with the other amendments made to the specification. No new matter has been added.

STATUS OF THE CLAIMS:

Claims 1 to 21 are cancelled.

Claims 22 and 29 have been amended.

Claims 22 to 37 are pending.

Claim 22 has been amended to replace the phrase "(a), (b), and (c)" with the phrase "(a), and (b)" by deleting the ", and (c)" phrase and appending the term "and" prior to the "(b)" phrase, in order to address the Examiners rejection to the same. Applicants right to equivalents of Claim 22 is reserved. No new matter has been added.

Claim 29 has been amended to replace the phrase "A recombinant host cell" with the phrase "An isolated recombinant host cell" by deleting the "A" term and appending the phrase "An isolated" prior to the "recombinant host cell" phrase, in order to address the Examiners objection to the same. Applicants right to equivalents of Claim 29 is reserved. No new matter has been added.

I. Miscellaneous

a. Public Access to and Viability of ATCC Deposit No. PTA-3161

Applicants representative hereby gives the following assurance by signature below:

Bristol-Myers Squibb Company, an assignee of the present application, has deposited biological material under the terms of the Budapest Treaty on the International Recognition of the Deposit of Micro-organisms for the Purposes of Patent Procedure with the following International Depository Authority: American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Virginia 20110-2209. The deposits comprise the cDNA sequences encoding the HGPRBMY25 polypeptide of the present invention. The deposit for HGPRBMY25 was made on March 7, 2001, and given ATCC Accession Number PTA-3161. In accordance with MPEP 2410.01 and 37 C.F.R. § 1.808, assurance is hereby given that all restrictions on the availability to the public of ATCC Accession Number PTA-3161 for the HGPRBMY25 clone will be irrevocably removed upon the grant of a patent based on the captioned application, except as permitted under 37 C.F.R. § 1.808(b), and that access to the deposit will be afforded to the Commissioner upon request.

Applicants representative also hereby gives the following additional assurance by signature below:

In accordance with 37 C.F.R. § 1.805 to § 1.807, assurance is hereby given that the viability of the deposit for HGPRBMY25, made on March 7, 2001, and given ATCC Accession Number PTA-3161, will be maintained during the pendency of the captioned application for a duration of at least 30 years or at least five years after the most recent request for the furnishing of a sample of the deposit is received by the ATCC, or whichever is longer; and that the deposit will be replaced if it should ever become inviable.

b. Objections to the Specification

The Examiner has objected to Applicants specification stating that "Applicant is required to update the specification by replacing the X and Y notations with appropriate SEQ ID Nos throughout the specification."

In response, Applicants have submitted a marked and clean copy of a Substitute Specification which replaces the X and Y notations with their respective and proper "SEQ ID NO:1", and "SEQ ID NO:2" references, respectively. The Substitute Specification also corrects a number of other typographical and grammatical errors identified by Applicants, including the deletion of URL or hyperlink references. No new matter has been added. Applicants point out that all amendments, including the amendments explicitly referred to individually herein, have also been entered by submission of the Substitute Specification for the convenience of the Examiner.

The Examiner has further objected to Applicants specification stating that "title of the invention is objected to because of the use of the word "novel", which begs the novelty of issued U. S. Patents. Any invention, when patented, is novel. There is no need to say it again in the title. It is suggested that the word "novel" be deleted from the title."

In response, Applicants have deleted the " NOVEL" term from the title of the instant specification to address the Examiners objection to the same.

II. Rejections under 35 U.S.C. § 101

a. The Examiner has rejected Claims 22 to 37 under 35 U.S.C. § 101, alleging that the claimed invention is not supported by either a specific and substantial utility or a well established utility. More particularly, the Examiner alleges that "The instant claims are directed to isolated polynucleotide encoding a polypeptide comprising SEQ ID No: 2 or an isolated polynucleotide comprising SEQ ID No: 1 belonging to an alleged G protein-coupled receptor HGPRBMY25 (claims 22-27). Claims are also drawn to vectors containing the polynucleotide sequences, host cells and methods of making the polypeptide (claims 28-30). In addition, claims are also drawn to heterologous nucleic acid encoding heterologous polypeptide (claims 31-37). These claims are drawn to an invention with no apparent or disclosed patentable utility... the specification fails to provide any sufficient information or evidence on the biological functions of the human protein encoded by the instantly claimed nucleic acid molecules...The invention also lacks a well-established utility. A well established utility is a specific, substantial, and credible utility that is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material. The sequence search of the prior art does not reveal a well-established utility for the nucleic acids. In fact, the nucleotides search of SEQ ID NO: 1 (nts 537-1523) of the present invention resulted in obtaining sequences that were 99.6% identical (see Appendix A1-3). However, these sequences have been annotated as GPCR or potential olfactory related G-coupled receptor (Accession NO: AAH31850, ABK16633 and ABK68612). In addition, amino acids sequence that is 98.8% identical to SEQ **ID** NO: 2 (see Appendix B1-7) of the present invention have also been annotated as GPCR or potential olfactory G-coupled receptor (Accession NO: AAU85266, AAG71674, AAU80511, AAU95725). Furthermore, Zang et al. (2002, Accession NO; Q8VGX9) describe a mouse olfactory receptor gene, which has about

89.3% identity to SEQ ID NO: 2 of the instant invention (see Appendix C). The discrepancy between the instant disclosure, that the protein encoded by the nucleic acid molecule is immune related protein and the annotation in the art for the similar protein as being an olfactory related GPCR casts doubts on the true biological functions of the protein encoded by the nucleic acids of the present invention. Thus, the assertion that the claimed nucleic acid molecules encoding a GPCR related to immune disorders, based on the mRNA expression profile, does not endow the claimed molecules with a specific and substantial utility. No art of record discloses or suggests any property or activity for the claimed molecules such that another non-asserted utility would e well-established for the claimed invention."

Applicants respectfully disagree with the Examiners and believe that the claimed invention is supported by a specific and substantial utility or a well established utility, and point out that Applicants have in fact taught and demonstrated that HGPRBMY25 is a functional G-protein coupled receptor in addition to elucidating its biological role. Specifically, the instant specification teaches that the HGPRBMY25 polypeptide is a G-protein coupled receptor (see pages 24 to 53, in general) based upon the strong homology to other members of the G-protein coupled receptor family (see pages 24 to 25; and Figures 2 and 5), the presence of 7 transmembrane domains within the encoded HGPRBMY25 polypeptide sequence (see page 25 to 30; and Figures 1A-B, and 3), in addition to the presence of a G-protein coupled receptor consensus sequence within the encoded HGPRBMY25 polypeptide sequence (see pages 44 to 46; and SEQ ID NO:20). Applicants assert that one skilled in the art would credibly believe that the HGPRBMY25 represents a G-protein coupled receptor based upon the strong homology to other known G-protein coupled receptors; the presence of the 7-transmembrane domains; in addition to the presence of the GPCR consensus sequence which is present in known functional G-protein coupled receptors. Both of the latter are signature features of functional G-protein coupled receptors and corroborated by the strong homology to known G-protein coupled receptors.

In addition, Applicants also point out that the instant specification teaches that the human HGPRBMY25 is a functional human G-protein coupled receptor capable of coupling via the promiscuous G-protein G-alpha 15 (see pages 30 and 31; and Example 5), in addition to teaching that the polypeptide localizes to the cell membrane (see pages 30 and 31; and Example).

Specifically, the specification states that "...in confirmation that the HGPRBMY25 polypeptide represents a novel GPCR, functional characterization experiments have shown that HGPRBMY25 functionally couples in the presence of the promiscous G-protein G alpha 15 via the NFAT/CRE response element using the methods described in Example 5 herein. Moreover,

immunocytochemistry experiments prove that HGPRBMY25 is not only expressed in transfected cell lines, but also localizes to the cell membrane." (see page 30 and 31)

Applicants believe the skilled artisan would readily recognize and credibly believe that the human HGPRBMY25 is a functional G-protein coupled receptor based upon the teachings of Applicants specification. Nonetheless, Applicants bring to the attention of the Examiner the Declaration under 37 C.F.R. §1.132 (referred to as the "Feder Declaration"; and submitted concurrently herewith), which provides experimental data confirming that the subject HGPRBMY25 polypeptide functions as a G-protein coupled receptor based upon its observed constitutive coupling to a signaling pathway known to be mediated by G alpha q/11 coupled receptors that activate NFAT response elements. The Declaration also provides experimental data demonstrating that the subject HGPRBMY25 polypeptide is a membrane bound polypeptide, and is expressed in the cells used in the described coupling assay. The data described in the Feder Declaration confirms the teachings of the instant specification on pages 30 to 31, and Example 5.

Demonstration that HGPRBMY25 is capable of functionally coupling to Gq/11 G-proteins is significant (see the "Feder Declaration") since it associates this receptor with the direct regulation of the well-established phospholipase C (PLC) signaling pathway. As the Examiner will appreciate, phospholipase C is a highly regulated enzyme that catalyzes the hydrolysis of phosphotidylinositol 4,5 bisphosphate to the second messengers inositol 1,4,5-triphosphate and diacylglycerol resulting in the activation of protein kinase C and the release of Ca2+ from intracellular stores.

It is known that all G-alpha q/11 G-proteins only activate the PLC-β isozymes, which is significant to HGPRBMY25 since such isozymes are enriched in immune tissues with PLC-β2 being restricted solely in hematopoietic cells. As the Examiner will appreciate, the NFAT response element is a transcription factor activated by antigen stimulation of the T-cell receptor which is primarily responsible for the coordinated induction of interleukin and cytokine genes during immune cell activation – activity that ultimately results in the proliferation, differentiation; and/or activation of hematopoietic cells. Activation of the NFAT response elements serves to functionally corroborate the immune-specific expression pattern of HGPRBMY25 (HGPRBMY25 was expressed in the lymph gland and the spleen at "approximately 160 and 100 times greater than that observed in majority of other tissue RNAs tested" see page 30 of the instant specification).

Applicants believe the teachings of the instant specification, and in particular, the teaching that HGPRBMY25 is a G-protein coupled receptor, the demonstration that HGPRBMY25 is a

functional G-protein coupled receptor based upon the teachings of the instant specification in addition to the Feder Declaration submitted concurrently herewith, the elucidation that HGPRBMY25 functionally couples via activation of NFAT response elements via G-alpha q/11 G-proteins and the subsequent activation of the well-established PLC second messenger pathway, in conjunction with the immune restricted expression pattern is sufficient to demonstrate to the skilled artisan that HGPRBMY25 would be useful for "regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages..." (see page 31). Applicants assert that HGPRBMY25 has a specific, substantial, and credible utility based upon the preponderance of the evidence described in the instant specification, and confirmed in the Feder Declaration.

Moreover, since HGPRBMY25 functions by activation of NFAT response elements via G-alpha q/11 G-proteins and the subsequent activation of the well-established PLC second messenger pathway, Applicants further assert that HGPRBMY25 has a well-established utility on account of it being associated with a well-established signal transduction pathway.

Applicants believe the Examiners rejection of Claims 22 to 37 under 35 U.S.C. § 101 has been overcome in consideration of the arguments presented supra, in addition to data provided in the Feder Declaration submitted concurrently herewith. Applicants respectfully request that the Examiner withdraw the rejection of Claims 22 to 37 under 35 U.S.C. § 101.

III. Rejections under 35 U.S.C. § 112, First Paragraph

a. The Examiner has rejected Claims 22 to 37 under 35 U.S.C. § 112, first paragraph. More particularly, the Examiner alleges that "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention."

Applicants disagree and believe the Examiner's rejection of Claims 22 to 37 has been overcome in consideration of Applicants arguments presented supra that demonstrate that HGPRBMY25 has a specific, substantial, and credible utility.

b. The Examiner has rejected Claims 22, 27, and 30 under 35 U.S.C. § 112, first paragraph, for lack of enablement alleging "enablement would not be commensurate in scope with claims 22, 27 and 30, which are drawn to complementary nucleotide sequences to the above mentioned polynucleotide"

Applicants disagree, however, in the sole interest of facilitating prosecution, Applicants have amended Claim 22 subclause "c" by substituting the phrase "(a), (b), and (c)" with the phrase "(a), and (b)". Applicants believe the Examiners rejection of Claim 22, 27, and 30 has been overcome in consideration of this amendment and respectfully request that the Examiner withdraw the rejection under 35 U.S.C. § 112, first paragraph.

> **c.** The Examiner has rejected Claims 29 to 30 under 35 U.S.C. § 112, first paragraph, alleging that these claims do "not reasonably provide enablement for" recombinant host cell comprising...", which encompasses the host cell, as it occurs in nature, for example, as a gene therapy patient."

Applicants disagree. However, in the sole interest of facilitating prosecution, Applicants have amended Claim 29 to recite the language recommended by the Examiner. Applicants believe the Examiners rejection of Claims 29 to 30 has been rendered moot in consideration of Applicants amendment.

> **d.** The Examiner has rejected Claims 34 to 37 under 35 U.S.C. § 112, first paragraph, alleging that it contains "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." More particularly, the Examiner alleges that "It is noted that the applicants have deposited the cDNA with ATCC (Page: 18). However, it is unclear if the deposit was made under the Budapest Treaty guidelines. If the deposit is made under the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific DNA encoding protein of SEQ ID NO: 2 has been deposited under the Budapest Treaty and that the DNA will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If the deposit is not made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. §§ 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that (a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request; (b) all restrictions upon availability to the publ,ic will be irrevocably removed upon granting of the patent; (c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effectiv~ life of the patent, whichever is longer; (d) a test of the viability of the biological material at the time of deposit will be made (see 37 C.F.R. § 1,807); and (e) the deposit will be replaced if it should ever become inviable. Applicant's attention is directed to M.P.E.P. §2400

> in general, and specifically to §2411.05, as well as to 37 C.F.R. § 1.809(d), wherein it is set forth that "the specification shall contain the accession number for the deposit, the date of the deposit, the name and address of the depository, and a description of the deposited material sufficient to specifically identify it and to permit examination. **The specification should be amended to include such information, however, Applicant is cautioned to avoid the entry of new matter into the specification by adding any other information**"

In response, Applicants representative has provided the required assurance in the "Miscellaneous" section of Applicants Reply *supra*. Applicants also point out that the instant specification already contain the "accession number for the deposit, the date of the deposit, the name and address of the depository, and a description of the deposited material sufficient to specifically identify it and to permit examination" on pages 8, 18, and 19. As a consequence, Applicants do not believe any additional amendment to the specification if required.

Applicants believe the Examiners rejection of Claims 34 to 37 have been overcome in consideration of Applicants assurances provided herein.

IV. Rejections under 35 U.S.C. § 112, second paragraph

> a. The Examiner has rejected Claims 22 to 37 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. More particularly, the Examiner has rejected Claim 22 "as being vague and indefinite because it is unclear how the applicant intends to get the complementary sequence of complementary sequence (see claim 22 (c)). Claims 23-31 are rejected insofar as they are dependent on the rejected claim 22."

In response, Applicants have amended Claim 22 (c) to replace the phrase "(a), (b), and (c)" with the phrase "(a), and (b)" to address the Examiners rejection of the same. Applicants believe the Examiners rejection of Claim 22 has been overcome as a consequence of this amendment. In addition, since Claims 23 to 31 depend from Claim 22, either directly or indirectly, Applicants believe the Examiners rejection of Claims 23 to 31 has also been overcome.

b. The Examiner has rejected Claims 22 to 37 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. More particularly, the Examiner has rejected Claim 34 as being "vague and indefinite for reciting the term "HGPRBMY25" because the full meaning of an acronym should be spelled out at its first use in any claim. Claims 35-37 are rejected insofar as they are dependent on the rejected claim 34."

Applicants disagree and point out that the term "HGPRBMY25" does not represent an acronym, but is rather the name assigned to the invention, in addition to the ATCC Deposit, by the inventors. As a consequence, Applicants believe the Examiners rejection of Claim 34, and dependent Claims 35 to 37, under 35 U.S.C. § 112, second paragraph is in error and respectfully request that the Examiner withdraw the rejection.

Applicants believe that all of the Examiners rejections and objections have been overcome and that all of the pending claims before the Examiner are in condition for allowance. An early Office Action to that effect is, therefore, earnestly solicited.

A two-month extension is hereby requested pursuant to 37 CFR §1.136(a). Please charge Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company in the amount of $450 for payment of the extension fee.

If any fee is due in connection herewith not already accounted for, please charge such fee to Deposit Account No. 19-3880 of the undersigned. Furthermore, if any extension of time not already accounted for is required, such extension is hereby petitioned for, and it is requested that any fee due for said extension be charged to the above-stated Deposit Account.

Respectfully submitted,

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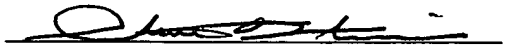

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